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PROBLEM OF IMMUNOLOGICAL SPECIFICITY

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Immunity is commonly defined as insusceptibility to infectious disease. Immunity can be natural, i.e., innate, or acquired during the life of the organism in question. Acquired immunity is distinguished by a fine degree of specificity that is determined by the presence in the organism of antibodies which specifically interact with only one substance, i.e., the antigen that has brought about their formation.

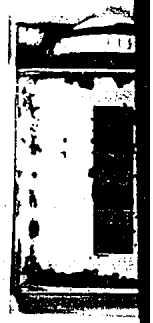
Not only microorganisms and the products of microorganisms function as antigens. The formation of specific antibodies takes place whenever any protein of any type is introduced into the organism of a warm-blooded animal. Consequently, the phenomena of specific immunity are not restricted to the field of microbiology alone. Immunity has a general biological significance. On the basis of I. I. Mechnikov's teaching, we understand specific immunity as the reaction of warm-blooded animals to any foreign protein possessing a different biological specificity.

The basis of all manifestations of life is formed by the proteins, with the aid of which metabolism takes place and forms a link between the organism and the surrounding natural environment. The most characteristic trait of proteins is their species specificity. The properties of the proteins of every living being are unique and cannot be duplicated in a single instance among the multitude of proteins of other species.

During the process of metabolism the organism inevitably comes into contact with proteins possessing a different species specificity. This takes place in connection with the consumption of foreign proteins as food or in the processes of parasitism and symbiosis. The interference of the foreign protein with the vital activity of the organism is not a matter of indifference by far to this organism: it may interfere in a severe manner with the normal course of its vital processes and change its specificity. The more active the manifestations of life, the more pronounced is the directing role of the indigenous specific proteins in the metabolism and the more harmful are the effects of foreign proteins.

The biological role of species specific proteins has been demonstrated in a particularly clear manner in work done by Soviet scientists. In investigations carried out originally at N.F. Gamaleya's laboratory (N.T. Gracheva) and later in greater detail by workers at V.T. Timakov's laboratory (D.G. Kudlay, N.S. Semchev, and others), the phenomena of modifiability resulting in species formation have been studied. If Baccilli coli are grown on a starvation medium which contains as the sole source of organic and nitrogen nutrition the proteins of bacteria of another species, for instance of baccilli of paratyphoid B, the B. coli acquire the basic properties of paratyphoid baccilli. Thus, under the effect of the protein of another species irreversible hereditarily fixed changes of the species characteristics of the microorganism take place.

The work mentioned clearly indicates that the interference of a foreign protein may be of decisive importance in determining the species to which the organism belongs.



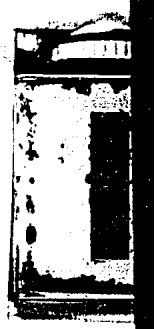
The fact that the interference of a foreign protein cannot be indifferent in nature has been clearly shown in work carried out at S. Ye. Bresler's laboratory. It has been shown there that proteolytic enzymes which are capable of splitting proteins may resynthesize them again from the products of scission when high pressures are applied and that the enzymatic resynthesis of proteins in this manner under the action of pressure restores the initial species specificity of the protein molecules, which has disappeared after enzymatic scission. If a mixture of proteins of different specificities is used in the experiment, their enzymatic resynthesis does not take place. The least admixture of protein products of extraneous origin makes entirely impossible the restoration of the proteins of the initial species.

The facts which have been cited make possible a deeper understanding of the general biological significance of immunity. In the light of these facts the phenomena of specific immunity appear as a vitally essential defense, i.e., a defense of the specific development of the organism against the action of foreign proteins which interfere with the regular course of the vital processes of this organism. In the body of warm-blooded animals a specific immunity is established because of the participation of specific, protectively acting antibodies in the processes on which immunity depends. The biological specificity of proteins shows distinctions not only with respect to species differences. Within a species the organisms are subdivided into groups and types, so that the immunological specificity is expressed in the existence of group and type distinctions between proteins derived from the same species. The interspecies differentiation of the characteristics of biological specificity is of outstanding importance.

From the standpoint of heredity and continuation of a species, it is important that the merging gametes should be similar or very close to each other as far as their species characteristics are concerned. At the same time, in order that the progeny be capable of life, the mutually fertilizing cells should not be identical in character. The internal differentiation of a species into groups, types, and individuals is for that reason a biological necessity. The more differentiated the species is within itself, the higher its vitality and the more favorable are the chances of its development.

The discovery that there is group and type specificity within the species in all living beings beginning with human beings and ending with bacteria has been of great importance for medicine. Identification of the causative factors of diseases such as dysentery, croupous pneumonia, meningitis, etc., from the standpoint of group characteristics makes the specific diagnosis of these diseases more precise and determines the nature of the therapeutic interference which is necessary. Classification of human beings with respect to groups and types makes certain that the right kind of blood is used in transfusions. The problem of individual specificity is a very real and essential one for contemporary surgery. The transplantation of complete organs and tissues used as a replacement can radically change contemporary medicine if the organs and tissues that are transplanted carry out to a full extent the functions of the original organs and tissues. The surgical technique of such operations has been developed in all essential respects (A.A. Vishnevskiy et al., N.P. Sinitsyn, and others.)

However, an organ which has been transplanted to an animal of the same species may be assimilated and function normally only for a period of several days. After this a phenomenon of incompatibility develops in it, which brings about a decay of the organ introduced from the outside and the death of the organism into which it has been transplanted. The incompatibility is determined by differences in individual specificity between the proteins of the donor and those of the recipient. Thus, the transplantation of organs and tissues is not primarily a surgical but an immunological problem.



The species, group, and individual specificity is the same as far as all proteins of a definite organism are concerned.

However, the organism is composed of a great number of proteins which fulfill different biological functions and have different chemical constitutions. Under the circumstances every individual protein exhibits, in addition to the species and group specificity which is common to all proteins of the organism, its own organic or functional specificity. The merging of species specificity and organic specificity within the protein molecule reflects the essential unity of the properties of uniqueness and differentiation within the organism. The existence of an organic or functional specificity was first discovered by I. I. Mechnikov, who has shown that after immunization of animals with the cells of definite tissues of another species, antibodies are formed which react specifically with these cells. These antibodies have been named Mechnikov's cytotoxins.

Organospecific sera have been utilized for the therapy of various pathological conditions. I.I. Mechinokov and G.D. Belonovskiy treated anemia with small doses of hemotoxins. A.M. Bezredka and after him A.A. Bogomolets reinforced the protective function of body cells by administering leukotoxic serum. In G.P. Sakharov's laboratory, pancreotoxic serum was successfully used for the therapy of diabetes. V.K. Khoroshko and other investigators used the neurotoxic serum for the therapy of schizophrenia.

Many experimental and clinical data indicate that it is possible to regulate purposefully the vital functions of the organism by applying immunological methods. However, these methods have not been widely applied in clinical practice and have not passed beyond the experimental stage because the organic specificity of antisera was always found to be merely relative in scope. The antibodies against definite tissues also interacted with the cells of other organs and tissues, although to a smaller extent. This is explained by the fact that the protein molecule has both organic specificity, which is characteristic for this protein only, and species or group specificity, which is common to all proteins of the organism from which it has been derived.

As a result of the immunization on an animal with one protein, not one but several antibodies of different specificities originate. The antiserum which is obtained is polyspecific rather than monospecific. It is necessary to remove from the antiserum the antibodies active against the general species antigen, thus leaving in it only organospecific antibodies. Then the monospecific serum which has been obtained will act only on a certain tissue of the organism without exerting any effect on other tissues.

The clinical application of monospecific cytotoxic sera is especially promising in cancer. The cancer tissue has the same species, group, and type specificity as all other tissues of the organism. In addition to that, it has a special cancer specificity. On immunization of animals with a human tumor, both anti-human antibodies and specific anticancer antibodies appear in the blood of the animal. The polyspecific antiserum which has been obtained in this manner reacts not only with cancer tissues, but also with normal tissues to almost the same degree.

In work carried out at our laboratory, A. K. Saakov succeeded in removing the general species antibodies with the result that a monospecific anticancer serum was obtained. Protein derived from normal human tissue was adsorbed on insoluble particles of dermatol. The normal dermatol antigen obtained in this manner exerts a specific effect in removing from the anticancer serum the general species antibodies, leaving behind only the cancer antibodies. The monospecific anticancer serum thus obtained is effective as a specific reagent for cancer protein. Using the same method, one may obtain monospecific sera active with respect to the most diverse tissues.

Using the monospecific anticancer serum, A. K. Saakov demonstrated that tumors of different localization (cancer of the stomach, cancer of the uterus, cancer of the lung) have the same cancer specificity. It has also been established in this work that not all proteins contained in the tumor are cancer proteins. One may isolate a definite protein fraction which reacts with antiserum much more intensively than the total initial cancer extract (V. I. Sachkov).

The possibility of exerting a directed effect on the growth of the cancer tumor by means of immunological methods has been experimentally proven at our laboratory. V. I. Sachkov has shown that introduction of the anticancer serum into mice with a grafted tumor inhibits the growth of the tumor and prevents the development of metastases after removal of the tumor by surgical means. V. N. Dobrokhotov has shown that the anticancer serum exerts a specific effect in inhibiting the cell division within the cancer tumor that has been grafted on mice. These results have been fully confirmed in work by S. V. Sukhorukikh, who used another method in work carried out at I. N. Mayskiy's laboratory.

The coexistence in a single protein molecule of species specificity and functional specificity has also been established as far as bacterial proteins are concerned. This fact is of importance in the production of bacterial vaccines. The organism of a bacterium is very complex. It possesses manifold vital functions which are carried out by different proteins; however, all proteins of the bacterial cell have the same species and group specificities and bring about the formation of general species antibodies on immunization.

In view of the fact that the proteins of bacteria differ among themselves as far as their functional specificity is concerned, the antibodies active against these proteins will not be the same.

The property of bringing about immunity in animals and human beings is not by far an inherent characteristic of all bacterial proteins: only some of them have this property. For that reason, not every antibody the action of which is directed against the species specificity of a microorganism will be active immunogenically.

The corpuscular vaccine has outlived its usefulness because of its imperfection. It consists of extremely diverse proteins, which are not of equal value in their immunogenicity. The chemical vaccine is replacing it. The chemical vaccine consists of bacterial proteins which have the property of immunogenicity and are devoid of an admixture of ballast proteins, although the ballast proteins have the general species specificity of the microorganism. Mechnikov has taught us to understand immunity as a general biological phenomenon. Soviet immunology is developing in accordance with this percept, as shown by the work of a number of scientific groups. The multiplicity of the possibilities for the utilization of the phenomena of immunity in clinical practice can be properly evaluated only from the general biological standpoint.

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